PATHOGENESIS OF INFANTILE SCURVY: AN HYPOTHESIS.*

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I. Etiology. Originally infection and toxemia played prominent parts in the theoretical etiology of scurvy, but during the past two decades there has been practically universal agreement among individuals working on the problem of scurvy that it is not due to an infection or to a toxemia, but to the destruction of some substance in the diet whose presence is necessary to prevent the development of the characteristic scorbutic symptoms. However, during the past year Jackson and Moody[30] reported observations which, according to McCollum,[44] are suggestive of the presence of a toxic substance of bacterial origin injuring the bloodvessels. McCollum[44] himself very recently stated that he is convinced that guinea-pigs on a diet of oats and milk suffer from scurvy because of the constipating character of the diet. I personally doubt, however, whether McCollum's guinea-pigs had only scurvy, as he characterizes his animals as having badly swollen joints and hemorrhages of the gums. These symptoms in the experience that I have had with some 150 scorbutic guinea-pigs during the past year and a half do not seem to me to be characteristic enough to permit a diagnosis of scurvy. It has been my experience, both in guinea-pigs fed according to the direction of Holst and Fröhlich[27] on the one hand and Jackson and Moore[29] on the other, that the animals fail to show what I should wish to call hemorrhages of the gums. This experience coincides with that of Holst and Fröhlich,[27] who did not find in their pigs hemorrhages of the gums as we see them in the human being. They did find, however, that the molar teeth became loose and were readily extracted. It seems to me probable that the beneficial results which McCollum and Pitz obtained by liberally dosing their guinea-pigs with liquid petrolatum will more readily fit into the clinical, therapeutic and pathogenetic picture of rickets or pseudorickets, as we know them at the present moment, than of scurvy. As Hart [15] [16] [17] states, it is impossible to know without a microscopic examination of the bone whether in scurvy cases showing swellings that resemble those seen in rickets only one disease or both diseases are present. I think, however, that this statement of Hart's may in certain cases be modified by the roentgen rays. Aside from McCollum and Pitz and Jackson and Moore, most men, such as Funk,[11] [12] Vedder,[52] Braddon and Cooper,[3] Holst and Fröhlich,[27] Schaumann,[47] Hart,[15] [16] [17] Hess,[19] [22] Fröhlich,[10] Fürst,[14] Budd and

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Busk,[14] and others, are of the opinion that the disease is a "deficiency" disease, due to an absence or inaction of one of the so-called "vitamines," "accessory growth factors," or one of the known food constituents.[43]

II. Clinical Picture. The clinical picture of scurvy has been controlled until recently by two symptoms, namely, hemorrhages into the bones and tissues and rarefaction and swelling of the osseous system. In 1914 Darling,[8] however, in his articles on "The Pathological Affinities of Beriberi and Scurvy," called attention to the distinct similarity between scurvy and beriberi in the production of some symptoms. He pointed out the presence in scurvy of exaggerated reflexes, tachycardia and dilatation of the heart. On microscopic examination he found fatty degeneration of the heart muscles and also degeneration of the vagus, while the other heart nerves were free from any lesion whatsoever. According to Lesage,[33] he and various other French authors as early as 1906–8 recognized the hyperesthetic form of scurvy which at times was clinically negative in every other respect and was diagnosed by its prompt response to antiscorbutic treatment. At the beginning of this year Hess[22] reported similar findings. So at the present time we have, from a clinical stand-point, symptoms that are referable to changes in the bloodvessels, in the osseous system, the nervous system, and the muscular system.

III. Pathogenesis. Hart [15] [16] [17] states that while on the one hand there is no doubt as to scurvy being a disease *sui generis*, yet there is, on the other hand, no settled opinion as to whether one and the same agent or process is responsible for the changes in the bones and the bloodvessels or whether they are due to different agents or whether they are interdependent upon each other. But it has seemed to me, in view of the known data regarding the pathology, chemistry and symptomatology of scurvy on the one hand, and regarding the important function played by calcium in bone growth, nerve conduction, vessel sealing, and cell permeability on the other, that all of these different system symptoms might be explained on the common basis of an interference with one or more of the normal functions of calcium and its physiological anion in the osseous system, vascular system, nervous system, muscular system and probably other systems.

So I have imagined the following:

1. That all of the symptoms of scurvy as we know them today may be explained on the common basis of a primary or secondary interference with one or more of the normal functions of calcium, alone or in conjunction with its physiological anion, a condition which I am pleased to call *a partial defunctioning of calcium and its physiological anion.* The work of Heubner[24] and Lipschütz,[34] namely, shows that for the ascorbutic development of the osseous system the presence of phosphorus in sufficient quantity is necessary.

2. That in scurvy as we see it occur in infants this defunctioning is caused by a substance produced through a break in the metabolism of carbohydrates, whatever their original source may be.[52]

3. That the break in carbohydrate metabolism occurs, as already suggested by Funk,[12] Braddon and Cooper[3] and others, as a result of the absence or inactivity or relative insufficiency or inadequacy or some physicochemical substance or "vitamine" essential to the establishment and performance of normal carbohydrate metabolism, possibly in the role of a catalyzer, as suggested by Schaumann,[47] as quoted by Holst and Fröhlich.[27]

4. That the defunctioning substance produced as a result of the break in the metabolism of carbohydrates due to a disproportionment between the carbohydrate supply on the one hand and the "vitamine" supply on the other, possibly is oxalic acid or some other agent that has a similarly strong affinity for calcium, and that after combining with calcium is soluble with similarly great difficulty.

There is, to my knowledge, no function whose perfect operation depends solely upon the presence and actions of only one and the same factor, and there is also, to my knowledge, no disease that is produced in every instance by the action of only one and the same factor.

A normal function can be pictured as an intact circle of links, and an abnormal function or disease has a circle of links broken in one or more of its links. Various and numerous circumstances and conditions will determine the link or links that usually break and produce a disease in a given environment, but occasionally in the same environment an entirely different link will break and, in consequence, just as successfully make impossible the performance of the same function in a normal manner and just as successfully develop the same disease, at least in its more important symptoms. Clinically the abnormal function may present itself to us in both instances in exactly the same picture, but it also is possible that the picture be different in some particulars while the same in others.

A good example of this in experimental scurvy has been given by the work of Heubner and Lipschütz referred to above. These authors fed dogs on a phosphorus-low diet and produced lesions, which, according to Schmorl,[48 34 24] are identical with the most characteristic lesions found in classically scorbutic bones, and yet the scorbutic bone lesions that we see in infants are often produced in a child on a diet whose phosphorus content is high rather than low, and in this latter instance, simply because, in all probability, for one reason or another, the phosphorus is prevented from performing its normal function in bone growth. This work of Lipschütz and Heubner, I believe, proves that phosphorus, at least so far as normal bone growth is concerned, is just as necessary as is calcium, and so I think that one can readily agree with the statement made by Masslow,[41] quoted by Baumann and Howard,[2] namely, that in the pathogenesis of the disturbances of the osseous system phosphorus plays a distinct role. Whether phosphorus joins calcium in a similar fashion in the function of sealing vessels or conducting nerve impulses, so far as the clinical picture and lesions of scurvy are concerned, is another question which cannot be answered at this time.

In connection with the work of Heubner and Lipschütz it should be stated that Walter Löb[39] is of the opinion that the presence of phosphates is necessary for normal glycolysis. However, as the sick dogs of Heubner and Lipschütz gained decidedly in weight while they were producing their own lesions it would seem, to say the least, that even the small quantities present in the diets of the dogs were sufficient to meet the glycolytic phosphorus needs of their bodies.

That calcium, however, has a distinct function to perform in the sealing of vessels and nerve conduction there can be no question, as the work of many authors shows. Chiari[5] has proved that saline cathartics act by increasing the permeability of the vessel wall by binding with their calcium and so extracting it from them. In another study it was possible for him and Januschke,[7] by a protective injection of calcium, to prevent the formation of an exudate on the conjunctiva of a rabbit into whose eye a drop of mustard oil was dropped. Overton,[46] quoting Herbst, states that the sealing substance in the tissue cells of certain animals is loosened by the removal of calcium and tightened by the readministration of calcium, and Januschke[36] was able to prevent the appearance of the usual and characteristic pleural exudate in iodin poisoning in dogs by the giving of calcium. Sir A. E. Wright[57] also found that calcium could prevent the development of certain urticarias, and he was inclined to attribute this beneficial effect of the calcium to the increased coagulability of the blood produced by it. Chiari and Januschke[7] took up this point and proved that the vessel-sealing function of the calcium was not the same as the one it performed in the coagulation of the blood; in other words, that it could perform the one without performing the other. These authors proved this by injecting hirudin into a rabbit that had been pretreated with calcium. Two hours later mustard oil was dropped into the eye and no exudate resulted, even though the coagulation time of the blood was kept distinctly below normal by the hirudin.

Hess[19] has shown that infants with scurvy show on the one hand a practically normal coagulation time, and on the other an increased permeability of their vessel walls as tested by the capillary test. While, as Hess states, this test is not pathognomonic of scurvy, as it occurs in many other conditions, yet it seems to me that its apparently constant presence in a marked form in scurvy makes it speak for the existence of an increased permeability of the vessel walls in scurvy. Holst and Fröhlich[27] fed their guinea-pigs calcium in different forms without getting any beneficial effect. Likewise

Ingier[23] did not succeed in checking the development of the scorbutic phenomena in pregnant guinea-pigs by adding phosphorated cod-liver oil to the diet, and Hess[19] reports the same negative results with infants. I also have given large doses of cod-liver oil with tricalcium phosphate to a florid case of scurvy absolutely without any beneficial effect (5 c.c. of cod-liver oil containing 20 per cent. tricalcium phosphate, twice daily for eight days). So that it is clear that the lessened permeability of the vessel wall in scurvy is produced in a manner that, in some particular at least, is different from that operating in the experiments carried out by Chiari and Januschke[5 7 31] and others.[32] Nevertheless, it is true that the vessel walls in scurvy are more permeable than normal, and also that calcium plays an important part in sealing the vessels, and so, in view of the additional fact that a disturbance in the calcium metabolism exists in scurvy, it still would seem possible that somehow an interference with the vessel-sealing function of calcium is responsible for the increased permeability of the vessel walls in scorbutic infants.

Chiari and Fröhlich[6] have further demonstrated that the autonomic nervous system is stimulated by the removal of calcium. This removal of calcium was produced by oxalates, and Januschke[31] showed that calcium antagonized this action of oxalates. H. H. Meyer,[45] in a short address referring to the work of the just-mentioned authors, states, "Our experiments prove two things: (1) a sedative action of the calcium on the vegetative nerve apparatus, and (2) a lessening of the permeability of the vessel wall."

Burridge,[4] in his very important experiments "On the Localization of the Calcium and Potassium Salts Concerned in the Mediation of the Action of the Vagus Nerve on the Heart of the Frog," definitely has found that "calcium salts are essential to complete passage from the preganglionic nerve fibers to the heart ganglia and that potassium salts favor the action of the terminal structure concerned in vagus action." He also states that the calcium salts, mediating the action of the vagus nerve on the frog's heart, form an integral part of the structure, whatever it may be, on which the nicotin acts. He further quotes the work of Chiari and Fröhlich, Meyer and Januschke, mentioned above, and that of Elliot,[4] who pointed out certain analogies between the synapses of the autonomic nervous system and the nerve endings of skeletal muscles. So these experiments also prove not only that calcium has an important function to perform in the transmission of nerve impulses, but that its defunctioning can produce symptoms such as we see presented in the heart and in the nervous systems of patients ill with scurvy and beriberi. Finally, it is well to call attention to the extremely important work of Jacques Loeb[35 36 37 39] and his co-workers regarding the function of calcium and other salts in cell permeability and irritability. He has proved[37] for calcium that the two functions are not the same and that in order to perform one certain conditions must be different than are present for the operation of the other.

None of the cases of scurvy that I personally have seen have shown a hyperexcitability to the galvanic current, and none of the cases of spasmophilia that I have tested have shown an increased permeability of their vessel walls, proving that while in each case there is a disturbance in the function of calcium, yet the clinical reaction to the same tests may be entirely different in each case. Of course, cases will be, or possibly have been, observed that show signs both of scurvy and spasmophilia.

Additional and important insight into the pathogenesis of the disease under discussion has been obtained by the observations of Lust and Klocman[40] on the one hand and through those of Bahrdt and Edelstein[1] on the other. The former found in studying the metabolism of a marked case of scurvy in an infant that during the active stage of scurvy there was a retention of the minerals investigated by them, namely, calcium, phosphorus and chlorin, especially that of the calcium, and that during the convalescent period of the same case there was a negative balance produced by an excessive excretion of the same salts, and finally that in the stage of healing, while the total ash and phosphorus balances were positive, the calcium balance remained still negative This discovery by Lust and Klocman finds corroboration in the microscopic and roentgenologic study of scorbutic bones. As is well known, Hoffmann,[26] [40] Schmorl,[48] [34] and other pathologists have described the presence of an increase rather than a decrease of the preparatory zone of calcification. Hoffmann[40] [26] even speaks of a calcium congestion, and Fränkel,[9] [40] with the roentgen rays, first called attention to the presence of the more or less broad, white line at the junction of the epiphysis and diaphysis of the long bones, and showed that this line disappears extremely slowly and is, as a matter of fact, still present when otherwise from a clinical stand-point the child seems perfectly well.

Bahrdt and Edelstein,[1] however, in the chemical analysis of bones from a marked case of scurvy, made discoveries which at the first glance seem to contradict those of Lust and Klocman.[40] Instead of showing an increase in the calcium and phosphorus content of the bones, as one might have expected from the findings of Lust and Klocman, they found a distinct deficit in calcium and phosphorus of the bones and muscles, with an increase in the water-content and possibly also in that of sodium and potassium. They also believe that the sodium and potassium of the liver and kidney were somewhat decreased while the calcium content of these organs was normal if not above normal. These authors state that their findings would indicate that the kidney and the liver, on the one hand and the bones and muscle on the other, take opposite positions in the calcium metabolism. They are not so sure as to the application of this statement to phosphorus, as it was found normal in all of the internal organs examined and also in the muscles.

Although the two findings of these two groups of authors seem to contradict each other, yet it seems to me perfectly possible that they do the opposite. The microscopic picture of scorbutic bones shows an increased deposition of calcium along the epiphyseal line but an increased porosity in the rest of the bone, especially in the diaphysis. This histological picture corresponds, as already stated above, with the roentgenologic, and I should think it perfectly plausible to assume that this condition is produced by a continuance of the normal function of bone resorption and a synchronous breaking-down of the normal function of bone development. That this latter in scurvy is not due to a deficiency in calcium is clearly proved by the miscrocopic picture and the roentgenological pictures which show an increase in the layer of calcification at Fränkel's line. In other words, while there is a certain amount of calcium being deposited at the part of the bone at which endochondral growth takes place under normal conditions, there is, nevertheless, in all probability not as much calcium in the whole bone at a certain advanced stage of scurvy as there would be in the normal, because in the first place the bone has ceased to grow either entirely[20] or at any rate not as markedly as under normal conditions, and in the second place the normal process of resorption is going on, producing a rarefaction and brittleness, with consequent loss of material. So it should be perfectly possible to find in the same child (1) an excess of calcium at the end of the bone in Fränkel's white line, (2) a reduction in the amount of calcium in the bone as a whole, such as Bahrdt and Edelstein found, and (3) a positive calcium balance, such as Lust and Klocman found, if but one thing happens, namely, that for some reason or other a holding down of calcium occurs in other parts of the body besides in parts of the bones. That there can be such a retention is indicated by the experience of Lust and Klocman, and even by the findings of Bahrdt and Edelstein themselves, who found a relative increase in the calcium content of the liver and kidney. An observation which I had occasion to make in a scorbutic child during June, 1916, also speaks in favor of a salt retention during the active stage of the disease. This child showed a marked difference between the water excretion by the kidney during the active and during the convalescent stages of the disease.

The chart below gives the details and shows that there was during the active stage a marked reduction in the amount of water excreted by the kidneys, which was not accompanied by a net increase in weight or by any significant change in the stools. Neither was there an influential change from the normal in the temperature chart, and the outside temperature was distinctly lower than it was during the stage when orange juice was given. The giving of orange juice markedly increased the urinary output

TABLE SHOWING URINE EXCRETION, ETC., DURING SCURVY.

Date, 1916.	Mean daily temperature.	Mean daily group, temperature.	Mean daily relative humidity.	Mean daily group, relative humidity.	Drugs.	Total fluid intake in 24 hours, including O. J. when given, c.c.	Average daily group intake, c.c.	Urinary output in twenty-four hours, c.c.	Average daily group urinary output, c.c.	Average daily urinary output, per cent.	Average daily group, urinary output, per cent.	Stools.	Body temperature.	Body weight grams.
June 22	60	65.7	61	66.8	None	1000	751.3	265	167.2	26.5	20.9	1 N	36.8-37.0-36.8	6570
23	64		56		"	720		65		9.0		1 E	36.9-36.8-37.1	6610
24	72		60		"	520		69		13.2		1 N, 1 sl. thin	37.4-38.2-37.2	6600
25	66		70		"	980		190		19.3		1 N, 1 sl. thin	36.8-37.1-36.8	6660
26	69		58		"	422		26		6.1		2 N	36.5-37.1-36.5	6590
27	65		83		"	740		145		19.5		1 N	37.0-37.2-37.0	6370
28	62		86		"	760		355		46.7		1 N, 1 choppy	37.0-37.4-37.0	6440
29	66		68		"	760		205		26.9		1 N	36.5-37.5-37.0	6480
30	68		60		"	860		185		21.5		1 N	36.6-37.4-37.4	6530
July 5	70	69.0	70	67.0	"	480	400.0	11	45.5	2.3	13.65	1 N	37.3-37.9-37.0	6350
6	68		58		"	320		80		25.0		2 N	37.3-37.8-37.5	6300
7	70		56		Pot. cit. 4x1 gm.	580	580.0	128	149.7	22.6	26.35	1 N	37.3-37.5-37.0	6260
8	72	70.5	72	69.0	"	620		88		14.1		2 N	37.5-38.0-37.4	6220
9	68		78		"	620		203		32.7		0	37.0-37.4-37.3	6250
10	72		70		"	500		180		36.0		2 choppy	37.3-38.3-37.5	6180
11-13	..		..		None	....		...		....		On the 11th:	37.3-38.8-38.8	6270
14	77	77.2	72	79.2	Na cit. 4x1 gm.	400	542.8	65	168.5	16.2	31.4	2 N	37.4-37.2-37.2	6200
15	81		64		"	470		200		42.5		0	37.7-37.7-37.3	6270
16	74		78		"	640		210		32.8		1 N	37.0-37.0-37.0	6220
17	75		86		"	440		175		39.7		2 N	36.8-37.3-37.3	6230
18	76		88		"	600		255		42.5		0	37.3-37.3-37.1	6090
19	80		77		"	530		160		30.1		1 choppy	37.3-37.2-37.1	6100
20	78		90		"	720		115		15.9		1 N	36.0-36.8-37.4	6160
21	76	77.0	68	61.1	Off. " On orange juice	?	835.0	420	320.0	....	40.15	......	36.8——36.8	6120
22	74		54		O. J. 60 c.c.	520		245		47.1		1 N	36.8-37.4-37.0	6080
23	76		59		" 90 "	970		310		31.9		1 N	37.2-37.2-37.2	6000
24	77		56		" 90 "	960		345		35.9		1 N	37.2-37.8-37.3	6060
25	78		68		" 90 "	1030		335		32.5		1 N	38.3-37.5-37.0	6090
26	78		60		" 90 "	1020		415		40.6		1 N	36.9-37.1-37.0	6150
27	80		62		" 90 "	510		270		52.9		1 N	37.0-37.3-37.3	6250

from 20 per cent. of the intake to 40 per cent., even though at this time the outside temperature was distinctly higher (14.1° F.). And in the face of this increased urinary excretion the infant made a net gain in weight, showing, just as the general appearance of the infant did, that the body was again working in a more normal fashion. Surely the simplest interpretation that can be given to this observation of decreased water output by the kidneys is a retention of salts by the body, either as a protective measure or simply as a result of hindered salt excretion, and that the water was given off mainly by way of the lungs.

This finding seems especially significant in view of the fact, as can be seen from the chart, that the giving of potassium citrate had only a little effect upon the urinary excretion. The amount of urine passed within twenty-four hours, however, notwithstanding the increase in outside temperature, was somewhat more increased by the giving of large doses of sodium citrate, and both in this case and in another it was observed that there also was a distinct but temporary improvement in the general condition of the scorbutic child after the administration of this salt; so marked was this in the one instance that the gums became distinctly reduced and pale, only, however, to get worse again in the face of the continued administration of the drug. The general behavior of the child improved within twenty-four hours, the gums were pale and decidedly reduced after 3 x 24 hours, and after remaining so for an additional 2 x 24 hours became abruptly worse again without any change in the therapy having been instituted in the meantime.

This same decrease in urinary excretion in the water output by the kidneys seems to occur in guinea-pigs getting scurvy on a diet of oats and water, for frequently I find in my notes the observation recorded that the sawdust pens of these animals at about the second week of the disease were especially dry and clean, and since having made the above-described observation in the infant with scurvy I have had occasion to ask four mothers of scorbutic infants regarding this symptom, and they all state that the baby "did not wet nearly as much since it had been sick as it did when it was still well." If this observation is confirmed and found to be present in most cases of infantile scurvy it will represent an addition to the clinical symptomatology of scurvy.*

Very recently Bauman and Howard[2] in their study of the mineral metabolism of normal and scorbutic guinea-pigs, reported findings which are in contradiction to those reported by Lust and Klocman for their infant. They found, namely, that all of the elements, except magnesium and chlorine, showed a negative balance during the scurvy period.

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* Since this article was presented, A. F. Hess (Infantile Scurvy: V. A Study of Its Pathogenesis, Am. Jour. Dis. Child., 1917, xiv, 337) has expressed the opinion that the increased pouring out of water by the kidneys after the administration of orange juice was due to a simple diuretic effect of the orange juice. However, from the experience obtained in this case with the administration of large doses of potassium citrate, which is the classical diuretic and much more effective than sodium citrate, it would hardly seem that Hess's interpretation were correct.

There can be no question that clinical experience with infantile scurvy points strongly to the carbohydrate high foods, everything else being equal, as being the most prominent factors concerned in the production of the disease. As already stated, Funk[12] and Braddon and Cooper[3]—the latter for beriberi—believe that the greater the amount of carbohydrate content of the food the greater will be the amount of "vitamine" required to keep up a normal carbohydrate metabolism, and the sooner the body supply of "vitamines" will be exhausted, especially if by various means, principally by heating, the "vitamines" present in any food are made useless.

At the time when Braddon and Cooper's[37] article appeared I had occasion to see a thirteen-months-old infant in a state of malnutrition and ill with a distinct clinical scurvy. This infant had been fed on various kinds of foods since its second month, but during the three months previous to his coming to me he had received, according to the mother, nothing but raw milk diluted with water, together with enormous amounts of Mellin's Food (sixteen heaping tablespoons). I questioned the mother carefully as to the manner in which she had warmed the bottle and how she had prepared the milk, but could only come to the conclusion that she had not warmed the bottle differently than is desirable. This made me feel at the time that this infant represented a counterpart to Braddon and Cooper's pigeons, and I still think so.

In this connection the experiments of Mayer[42] and Hildebrandt[25] are very suggestive, as these authors were able to prove a breaking down in the oxidation process of sugar in animals after having administered excessive doses of carbohydrates. And what is more, they have proved that under these circumstances at least a certain part of the oxidation of glucose stops with the production of oxalic acid, an acid which, as is well known, has an enormous affinity for calcium and with it forms a salt that is soluble with great difficulty.

However, all of the symptoms produced by these authors and others, such as Chiari, Chiari and Fröhlich, and Januschke,[5 6 7 31] by binding calcium through the administration of oxalic acid could be prevented or, at any rate, modified and lessened by giving calcium in sufficiently large doses, an experience that has not been met with in cases of scurvy that have received calcium and cod-liver oil in seemingly adequate doses—Hess,[19] Ingier,[28] and H. J. G. (see page 257). And then, as Sedgwick has shown, newborn infants excrete within twenty-four hours a much larger amount of oxalic acid than do adults, and give evidence of no condition that can be compared with any of the known symptoms of scurvy.

So that while there are many clinical and experimental data that seem to speak strongly against the assumption that oxalic acid is responsible for the defunctioning of calcium and its corresponding physiological anion, it has nevertheless seemed worth while to me to try to settle this question by resorting to every means possible to try to find oxalic acid present in cases of scurvy as a calcium fixer, because not only would its presence explain the production of the various symptoms described in the earlier part of the paper as a result of defunctioning calcium and its physiological anion in the bones, the vessels and the nervous system, etc., but also the rapid and marvelous disappearance of the symptoms just mentioned by the oxidation of oxalic acid in the presence of the physicochemical substance or "vitamine" necessary for normal and complete oxidation of carbohydrates and through its consequent primary release of calcium and its secondary release of other salts.

And it seems to me, in the face of the adverse experimental data mentioned above, as if, after all, oxalic acid could be responsible for the defunctioning of calcium and its physiological anion, if we assume that the production of the oxalic acid and its binding with calcium occurs within certain cells themselves, or in tissues that are poorly supplied with blood and lymph vessels, such as cartilage, both places where the solution of a salt like calcium oxalate would be distinctly less readily accomplished than, for instance, in the blood stream itself.

That the conditions for salt solubility in a given tissue system or, in other words, its fluid inflow and outflow, and the extensiveness of the system also may be a factor of decided importance in the production of the type and behavior of the different clinical, histological and chemical symptoms of scurvy, seems probable from a consideration of the location of the lesions in the vessels and in the bones.

It is certain that the most marked changes occur where bone growth is relatively greatest and where at the same time the blood supply is relatively smallest. So in the lower extremities the more severe lesions are located in the neighborhood of the knee, and in the upper extremity in the neighborhood of the wrists and shoulders, all parts of the extremities lying in the opposite direction of the nutrient artery. Then, the lesions limited to the vessels all clear up much more rapidly than those occurring in the bone, and in the bone again the lesions last to disappear are those in the region of Fränkel's white line, surely a part of the bone which has less blood-vessels than that near the periosteum, a fact that also can well explain why Fränkel's line persists much longer than any other one symptom of scurvy.

From the close dependence of the severity of the vessel lesion on its proximity to growing bone, one might believe that the substance which defunctionates calcium and its physiological anion is produced solely by the bone cells, the osteoblasts, and that the vessel lesions are produced by the vessel cells coming into contact with this agent during its passage in the blood stream. But the published accounts of hyperesthetic cases such as were described by Lesage[33] and of cases showing hematuria as the only symptom, make it more probable that cells of different systems may not be able to entirely oxidize carbohydrates in a normal manner. It also may be possible that the hematuria may be produced as a result of a change in the chemical form of the attacking agent during its excretion by the kidneys, although this does not seem plausible for other reasons. So taken all in all it does seem as if various cells, some for hereditary and some for acquired reasons, first break down and more completely than other cells in the performance of their carbohydrate metabolism and consequently show clinically recognizable signs of scurvy, either alone or in advance of cells located elsewhere. That, however, all vessel lesions in their entirety are not due solely to the breakdown of the carbohydrate metabolism of their own cells, would seem to be true from the close connection existing between the severity of the bloodvessel lesions on the one hand and of their proximity to the bones on the other. This is most beautifully demonstrated by the lesions occurring in the gums only when the teeth are erupting or have erupted; in other words, at a time when the alveolar periosteum is very active and when the gums have become firmly attached at the neck of the tooth to the tooth and to the periosteum.

Also periosteal bone formation is a much more vascular process than endochondral bone formation is, and this further explains the presence of the greatest hemorrhagic lesions along the periosteum.

At the present moment, however, I do not find myself in a position definitely to state that oxalic acid is or is not the defunctioning agent responsible for the production of the clinical symptoms of scurvy, even though I have diligently and persistently tried to prove its presence for more than twelve months. However, I expect to be able to report within the very near future.

It may be that another substance may be responsible for the clinical symptoms of this disease, but if this is so then it seems to me as if it must have the same powers regarding the defunctioning of calcium and its physiological anion that oxalic acid has, and the same *modus operandi.*

It is also possible that the defunctioning of calcium and its physiological anion does not occur through the action of the kind of substance indicated above or within the cell, or solely within the cell, but that it occurs in the cell membrane, at least partly so, and there, *via* the same or another *modus operandi*, affects the cell permeability in a manner as suggested by the interesting and important experiments of Jacques Loeb.[35 36 37 38] The observation made in the two scorbutic infants after the administration of sodium citrate might be interpreted in this manner.

Observations made by me in experimental work with a scorbutic infant and with pigeons ill with polyneuritis* make me feel that in all probability we shall find that the defunctioning agent is produced as a result of a broken-down carbohydrate metabolism due to a disproportionment within the cells between the carbohydrate supply on the one hand and the physicochemical substance, the so-called "vitamine," growth factor or known substance on the other.

These observations have shown that there is an immediate, distinct and marvelous change produced in the pigeons ill with polyneuritis by the administration of yeast, and in the scorbutic child by the administration of orange juice in the respiratory quotient† that can only be interpreted as indicating an immediate and marked rearrangement and readjustment in some known or unknown oxidative process of the body.

This observation is an added argument against the assumption of McCollum and Pitz,[44] that scurvy is produced in guinea-pigs as a result of constipation. Before any orange juice can possibly get down to the large intestines a definite and distinct change can be registered by the respiratory apparatus. And then constipation is not a part of the clinical picture of scurvy, as it does not occur with any kind of regularity or frequency in scorbutic infants, and the large intestine of my scorbutic guinea-pigs on oat-and-water diets have off and on been practically empty at necropsy.

The remarks regarding the observations obtained by studying the respiratory quotient in the scorbutic infant and in polyneuritic pigeons are also to be considered as having been made in the sense of a preliminary statement.

RÉSUMÉ. 1. An hypothesis is offered regarding the pathogenesis of infantile scurvy.

2. The hypothesis is divided into four separate parts, of which only the first is considered to be sufficiently based on experimental and clinical data to permit its exit out of the domain of pure hypothesis.

The second and third, the latter of which has been similarly and previously advanced by other authors, are considered to have as a basis experimental and clinical data that are distinctly suggestive, while the fourth is still purely hypothetical, although on its assumption it is possible to explain satisfactorily some of the clinical phenomena of scurvy that hitherto have had not even an hypothetical explanation.

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* Very suggestive data can be found in the work reported by MacArthur and Jones (Some Factors Influencing the Respiration of Ground Nervous Tissue, Jour. Biol. Chem., 1917, xxxii, 271), who studied the respiratory quotient of different parts of the central nervous system and found that the respiratory quotient is higher in white matter than in gray, and higher in the peripheral nerves than in the other portions of the nervous system.

† Ibid.

3. A report is made of a case of infantile scurvy which showed a marked reduction in the water output of the body through the kidneys without the presence of the usual and known causes for water loss *via* other channels, and which further showed a marked change toward a return to normal conditions by the administration of orange juice, indicating a protective salt retention or hindered salt excretion as the cause of the transfer of a good portion of the water excretion from the kidneys to the lungs.

The same condition seemingly was present in 4 additional cases of infantile scurvy as well as in scorbutic guinea-pigs on an oat-and-water diet.

It is suggested that the phenomenon observed is a part of the regular picture of infantile scurvy and represents an addition to the clinical symptomatology of scurvy.

4. A case of infantile scurvy is reported as being a counterpart to Braddon and Cooper's polyneuritic pigeons by having developed its symptoms on a diet of raw milk, modified, however, by dilution with water to one-half and by the addition of enormous amounts of carbohydrates in the form of Mellin's Food.

5. The experience of other authors regarding the inefficiency of cod-liver therapy and calcium therapy in scurvy is corroborated by absolutely negative therapeutic results having been obtained in a case of infantile scurvy upon the administration of tricalcium phosphate and cod-liver oil, indicating that a deficiency of calcium in the diet or in the body plays no primary role in the development of scurvy.

6. A report is made of a distinct but temporary improvement in the clinical picture of 2 cases of infantile scurvy upon the administration of large doses of sodium citrate. This observation suggests the possibility of the existence in the development of the clinical picture of infantile scurvy of a *modus operandi* similar to such as has been shown to exist in cell permeability and irritability by the researches of Jacques Loeb.

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